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(21) International Application Number: PCT/EP00/01773 (22) International Filing Date: 2 March 2000 (02.03.00) (30) Priority Data: MI99A000455 5 March 1999 (05.03.99) IT (71) Applicant (for all designated States except US): CHIESI FARMACEUTICI S.p.A [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): MUSA, Rossella [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). BILZI, Roberto [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). VENTURA, Paolo [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). CHIESI, Paolo [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). (74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milan (IT).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MODIFIED CARRIER PARTICLES FOR USE IN DRY POWDER INHALERS (57) Abstract <p>The invention relates to carrier particles for use in pharmaceutical compositions for the pulmonary administration of medicaments by means of dry powder inhalers. In particular, the invention relates to a novel technological process for obtaining a carrier modified so as to improve the efficiency of redispersion of active particles and hence increase the respirable fraction. After the treatment of the invention, the surface of said modified carrier particles can also be coated with a suitable additive so as to further improve the respirable fraction.</p>		

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MODIFIED CARRIER PARTICLES FOR USE IN DRY POWDER INHALERS

PRIOR ART

Inhalation anti-asthmatics are widely used in the treatment of reversible airway obstruction, inflammation and hyperresponsiveness.

5 Presently, the most widely used systems for inhalation therapy are the pressurised metered dose inhalers (MDIs) which use a propellant to expel droplets containing the pharmaceutical product to the respiratory tract.

10 However, despite their practicality and popularity, MDIs have some disadvantages:

i) droplets leaving the actuator orifice could be large or have an extremely high velocity resulting in extensive oropharyngeal deposition to the detriment of the dose which penetrates into the lungs;

15 ii) the amount of drug which penetrates the bronchial tree may be further reduced by poor inhalation technique, due to the common difficulty of the patient to synchronise actuation from the device with inspiration ;

20 iii) chlorofluorocarbons (CFCs), such as freons contained as propellants in MDIs, are disadvantageous on environmental grounds as they have a proven damaging effect on the atmospheric ozone layer.

25 Dry powder inhalers (DPIs) constitute a valid alternative to MDIs for the administration of drugs to airways. The main advantages of DPIs are:

i) being breath-actuated delivery systems, they do not require co-ordination of actuation since release of the drug is dependent on the patient own inhalation;

30 ii) they do not contain propellants acting as environmental hazards;

iii) the velocity of the delivered particles is the same or lower than that of the flow of inspired air, so making them more prone to follow the air flow than the faster moving MDI particles, thereby reducing upper respiratory tract deposition.

DPIs can be divided into two basic types:

i) single dose inhalers, for the administration of pre-subdivided single doses of the active compound;

ii) multidose dry powder inhalers (MDPIs), pre-loaded with quantities of active ingredient sufficient for multiple doses; each dose is created by a metering unit within the inhaler.

Drugs intended for inhalation as dry powders should be used in the form of micronised powder so they are characterized by particles of few micron particle size (μm). Said size is quantified by measuring a characteristic equivalent sphere diameter, known as aerodynamic diameter, which indicates the capability of the particles of being transported suspended in an air stream. Respirable particles are generally considered to be those with diameters from 0.5 to 6 μm , as they are able of penetrating into the lower lungs, i.e. the bronchiolar and alveolar sites, where absorption takes place. Larger particles are mostly deposited in the oropharyngeal cavity so they cannot reach said sites, whereas the smaller ones are exhaled.

Although micronisation of the active drug is essential for deposition into the lower lungs during inhalation, it is also known that the finer the particles, the stronger are the cohesion forces. Strong cohesion forces hinder the handling of the powder during the manufacturing process (pouring, filling). Moreover they reduce the flowability of the particles while favoring the agglomeration and/or adhesion thereof to the walls. In multidose DPI's, said phenomena impair the loading of the powder from the

reservoir to the aerosolization chamber, so giving rise to handling and metering accuracy problems.

Said drawbacks are also detrimental to the respirable fraction of the delivered dose being the active particles unable to leave the inhaler and remaining adhered to the interior of the inhaler or leaving the inhaler as large agglomerates; agglomerated particles, in turn, cannot reach the bronchiolar and alveolar sites of the lungs. The uncertainty as to the extent of agglomeration of the particles between each actuation of the inhaler and also between inhalers and different batches of particles, leads to poor dose reproducibility as well.

In an attempt to improve both the handling and the efficiency, the dry powders for inhalation are generally formulated by mixing the micronised drug with a carrier material (generally lactose, preferably α -lactose monohydrate) consisting of coarser particles. In such ordered mixtures, the micronised active particles, because of the electrostatic or Van der Waals interactions, mainly adhere to the surface of the carrier particles whilst in the inhaler device; on the contrary, during inhalation, a redispersion of the drug particles from the surface of the carrier particles occurs allowing the formers to reach the absorption site into the lungs.

Nevertheless, the use of a carrier is not free of drawbacks in that the strong interparticle forces between the two ingredients may prevent the separation of the micronised drug particles from the surface of the coarse carrier ones on inhalation, so compromising the availability of the drug to the respiratory tract. The surface of the carrier particles is, indeed, not smooth but has asperities and clefts, which are high energy sites on which the active particles are preferably attracted to and adhere more strongly; because of such strong, interparticle

forces, they will be hardly leave the surface of the carrier particles and be dispersed in the respiratory tract.

Therefore the features of the carrier particles should be such as to give sufficient adhesion force to hold the active particles to the surface of the carrier particles during manufacturing of the dry powder and in the delivery device before use, but that force of adhesion should be low enough to allow the dispersion of the active particles in the respiratory tract.

The prior art discloses several approaches for manipulating the interparticle interactions between the drug and the carrier in ordered powder mixtures.

First, the carrier particles can be chosen according to their median particle size, taking into account the fact that a decrease in median particle size increases the adhesion force between drug and carrier particles.

GB 1,242,211 and GB 1,381,872 disclose pharmaceutical powders for the inhalatory use in which the micronised drug (0.01 - 10 μm) is mixed with carrier particles of sizes 30 to 80 μm and 80 to 150 μm , respectively; said mixtures can also contain a diluent of the same particle size as the micronised drug.

The deaggregation of the active ingredient from the carrier during inhalation can also be made more efficient by modifying the surface properties of the carrier and/or by addition of a fine fraction (<10 μm), preferably of the same material of the carrier (Podczek F. *Aerosol Sci. Technol.* 1999, 31, 301-321; Lucas P. et al *Resp. Drug Deliv.* 1998, VI, 243-250).

GB 2,240,337 A discloses, for example, a controlled crystallization process for the preparation of carrier particles with smoother surfaces, and, in particular, characterized by a rugosity of less than 1.75 as measured

by air permeametry; in practice their smoothness is readily apparent under electronic microscope examination. The use of said carrier particles allows to increase the respirable fraction of the drug (Kassem, Doctoral thesis of the London University, 1990).

EP 0,663,815 claims the use of carriers for controlling and optimizing the amount of delivered drug during the aerosolisation phase, consisting of suitable mixtures of particles of size $> 20 \mu\text{m}$ and finer particles ($< 10 \mu\text{m}$).

Staniforth et al. (WO 95/11666) combine both the aforementioned teachings (i.e. modification of the surface properties of the carrier and addition of a fine fraction) by exploiting the effects of a milling process, preferably carried out in a ball mill, referred to as corrasion (corrasion is a term used in geology and it describes either the effect of the wind on rocks and the filling of valley with stones during the ice age). Said process modifies the surface properties and it gets rid of the waviness of the carrier particles by dislodging any asperities in the form of small grains without substantially changing the size of the particles; the small grains, in turn, can be reattached to the surfaces of the particles either during the milling phase or after preventive separation followed by mixing, in order to saturate other high energy sites such as clefts. Said preliminary handling of the carrier causes the micronised drug particles to preferably link to the lower energy sites, thus being subjected to weaker interparticle adhesion forces.

Podcěk (*J. Adhesion Sci. Technol.* 1998, 12, 1323-1339), after having studied the influence of the corrasion process on the adhesion forces by blending the carrier with different percentages of fine particle fraction before

addition of the drug, concluded however that such process is not always sufficient to ensure effective redispersion but the latter also depends on the initial surface roughness of the coarse carrier particles.

Patent literature also suggests the use of powder formulations for inhalation wherein the adhesion between the carrier particles and the active ingredient particles is further reduced by addition of suitable amounts of suitable additives.

In WO 96/23485, particles are mixed with an anti-adherent or anti-friction material consisting of one or more compounds selected from amino acids (preferably leucine); phospholipids or surfactants; the amount of additive and the process of mixing are preferably chosen in such a way as to not give rise to a real coating, but instead a partial coating directed to the high energy sites. The carrier particles blended with the additive are preferably subjected to the corrasion process in a ball mill as disclosed in WO 95/11666.

OBJECT OF THE INVENTION

It has now been found, and it is the object of the invention, that it is possible to modify the surface properties of the carrier particles and simultaneously modulate their interaction with the micronised drug particles by producing in situ a fine fraction of the carrier itself, without submitting the coarse carrier particles to a milling process but by employing a conventional mixer.

The use of a mixer, which intrinsically assures milder conditions, allows to modify the surface properties of the carrier particles without significantly changing their sizes, crystalline structure and chemico-physical properties.

It has been indeed reported that the chemical

compounds preferably used as carrier, such as lactose, can undergo chemico-physical alterations, when subjected to mechanical stresses, such as milling (Otsuka et al. J. Pharm. Pharmacol. 43, 148-153, 1991).

5 Moreover, hard treatments such as corrasion may moderately reduce the cristallinity of the additives used (Malcolmson R et al. Respiratory Drug Deliv. 1998, VI, 365-367).

10 It has been also surprisingly found that, by virtue of the milder operative conditions of the invention, the fraction of fine particles of size larger than 10 μm is poor, as proved by the particle size analysis via laser diffractometry (Malvern). It is well known that only the fine fraction below 10 μm , once redistributed onto the
15 surface of the coarse carrier particles, is indeed responsible for the decrease of the interparticle forces, whereas the fine particles of size larger than 10 μm , contribute to decrease the flowability of the powder.

20 On the contrary, milling, as reported above, is a hard process which produces a fine fraction with a much wider particle size distribution which, in turn, could be detrimental for the flow properties of the mixture. Therefore, the powders made with carriers preventively subjected to milling processes could turn out to be not
25 flowable enough to be suitable for multidose inhalers. Accordingly, the carriers subjected to the milling process often require a further separation step in order to select the fine fraction suitable for being mixed with the coarse carrier particles and discard that one which can be
30 detrimental to the flow properties of the powder.

By operating according to the process of the present invention, the flow properties of the carrier are not significantly affected, as indicated by the Carr index as well as by the Flodex test. The process of the invention

allows therefore to avoid the further separation step of the fine fraction suitable for being mixed with the coarse carrier particles.

The mixing process of the invention, compared with the milling process as described in WO 95/11666, allows to remarkably reduce the time of treatment. In a preferred embodiment of the invention, carriers with suitable properties are indeed obtained after 30 minutes of treatment in a sigma blade mixer whereas, according to WO 95/11666, carrier particles should be milled for at least one hour and preferably six hours.

Finally, the process of the invention provides a carrier for dry powders for inhalation able of giving good performances in terms of respirable fraction of the drug as demonstrated by the examples reported.

Advantageously the carrier particles are treated in any mixer, of any size and shape, equipped with a rotating element. Preferably the carrier particles are treated in mixers constituted of a stationary or rotating body equipped with any rotatory element (blade, screw) or in the high energy mixers ("high-shear") and blended for a total time ranging from 5 to 360 minutes.

Even more preferably the carrier particles are treated in a sigma-blade mixer at a rate of 100-300 r.p.m and for 30 minutes.

The carrier particles may be constituted of any pharmacologically acceptable inert material or combination thereof; preferred carriers are those made of crystalline sugars, in particular lactose; the most preferred are those made of α -lactose monohydrate. Advantageously the diameter of the carrier particles lies between 20 and 1000 μm , preferably between 90 and 150 μm .

A further aspect of the invention relates to the preparation of carrier powders in which, after treatment in

a mixer, the carrier particles are mixed with suitable amounts, preferably from 0.05 to 2% by weight, of additives able of further reducing the drug-carrier interparticle forces, thereby increasing the respirable fraction.

5 The additives can be selected from those belonging to the class of the lubricants, such as metal stearates or to the classes of anti-adherent agents or glidants.

 The preferred lubricant is magnesium stearate, but stearic acid, sodium stearyl fumarate and sodium benzoate
10 can also be used.

 A further aspect of the invention are the formulations for inhalation obtained by mixing the active ingredient particles (with a mean aerodynamic diameter of less than 5 mm) with carrier powders obtained according to the process
15 of the invention.

 The preferred active particles will be particles of one or mixture of drugs which are usually administered by inhalation for the treatment of respiratory diseases, for example steroids such as beclomethasone dipropionate, flunisolide and budesonide; β -agonists such as salbutamol, formoterol, salmeterol, terbutaline and corresponding salts; anticholinergics such as ipratropium bromide. Any other active ingredient suitable for pulmonary and/or nasal delivery can be anyway used in these formulations.

25 The process of the invention is illustrated by the following examples.

EXAMPLE 1

a) Preparation of the carrier

α -Lactose monohydrate with a starting particle size
30 between 90 to 150 μ m is mixed for 30 minutes in a sigma blade mixer. At the end of the treatment, only a slight reduction of the particle size is observed.

 The Malvern analysis pattern referring to the particle size distribution of the carrier particles before (- -) and

after (----) the pre-mixing treatment is reported in Figure 1 whereas the relevant data are reported in Table 1.

Table 1. Particle size distribution (μm)

		Unmixed	Pre-mixed
5	Malvern d (v, 0.1)	100.4	61.4
	d (v, 0.5)	138.3	127.1
	d (v, 0.9)	197.8	187.7

b) Preparation of the beclomethasone dipropionate (BDP)/lactose binary mixture

10 The carrier powder obtained according to the process a) is mixed with such an amount of micronised beclomethasone dipropionate as to obtain a ratio of 200 μm of active to 26 mg total mixture.

c) Characterization of the mixture

15 The active ingredient/carrier mixture was characterized by its density and flowability parameters.

The poured density (d_v) and the tapped density (d_s) were calculated as follows. Powder mixtures (20 g) were poured into a glass graduated cylinder and d_v was calculated dividing the weight by the volume; d_s was calculated from the volume obtained after tapping the powder mixture 500 times using a commercially available apparatus.

25 The flowability was evaluated from the Carr's index calculated according to the following formula:

$$\text{Carr's index (\%)} = \frac{d_s - d_v}{d_s} \times 100$$

30 A Carr index of less than 25 is usually considered indicative of good flowability characteristics.

The flowability properties were also determined by using a Flodex tester. The determination is based upon the ability of the powder mixture to fall freely through holes of different diameters placed at the bottom of a cylinder.

The powder was poured into the cylinder via a powder funnel. The flowability index is given in millimetre diameter of the smallest hole through which the powder falls freely.

5 d) Determination of the aerosol performances.

An amount of powder for inhalation was loaded in a multidose inhaler (Pulvinal^(R) - Chiesi Pharmaceutical SpA, Italy).

10 The evaluation of the aerosol performances was performed by using a Twin Stage Impinger apparatus, TSI (Apparatus of type A for the aerodynamic evaluation of fine particles described in FU IX, 4° supplement 1996). The equipment consists of two different glass elements, mutually connected to form two chambers capable of
15 separating the powder for inhalation depending on its aerodynamic size; the chambers are referred to as higher (stage 1) and lower (stage 2) separation chambers, respectively. A rubber adaptor secures the connection with the inhaler containing the powder. The apparatus is
20 connected to a vacuum pump which produces an air flow through the separation chambers and the connected inhaler. Upon actuation of the pump, the air flow carries the particles of the powder mixture, causing them to deposit in the two chambers depending on their aerodynamic diameter.
25 When the air flow is 60 l/min, the aerodynamic diameter limit value, d_{ae} , for the deposition in the lower separation chamber is 6.4 μm . Particles with higher d_{ae} deposit in Stage 1 and particles with lower d_{ae} in Stage 2. In both stages, a minimum volume of solvent is used (30 ml
30 in Stage 2 and 7 ml in Stage 1) to prevent particles from adhering to the walls of the apparatus and to promote the recovery thereof.

The determination of the aerosol performances of the mixture obtained according to the preparation process b)

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was carried out with the TSI applying an air flow rate of 60 l/min for 5 seconds.

After nebulization of each dose of the dry powder in the Twin Stage Impinger, the apparatus was disassembled and the amounts of drug deposited in the two separation chambers were recovered by washing with a solvent mixture, then diluted to a volume of 50 ml in two volumetric flasks, one for Stage 1 and one for Stage 2, respectively. The amounts collected in the two volumetric flasks were then determined by High-Performance Liquid Chromatography (HPLC). The following parameters, as mean and relative standard deviations (RSD) of the values obtained from three inhalers, by actuating 5 shots from each inhaler, were calculated: i) the fine particle dose (FPD) which is the amount of drug found in stage 1 of TSI; ii) the emitted dose which is the amount of drug delivered from the device recovered in stage 1 + stage 2; iii) the fine particle fraction (FPF) which is the percentage of the emitted reaching stage 2 of TSI.

The results in terms of technological parameters and aerosol performances are reported in Table 2, in comparison with a similar preparation obtained by mixing the active ingredient with α -lactose monohydrate lactose 90-150 μm not pre-treated in the mixer (standard preparation).

Table 2

Standard Preparation		Preparation of Example 1	
		Technological Parameters	
	Apparent Density (g/mL)		
5	- Poured	0.71	0.75
	- Tapped	0.80	0.90
	Flodex test (Ø 4mm)	4	4
	Flow rate through		
	Ø 4mm (g/min)	67	46
10	Carr Index (%)	11	17
		TSI test	
	Mean weight (mg)	22.8 (3.3)	25.6 (2.6)
	Emitted dose (µg)	184.0 (3.3)	165.8 (6.9)
	FPD (µg)	31.0 (50.9)	37.4 (8.9)
15	FPP (%)	16.9 (53.2)	22.7 (10.6)

The results show that the flowability properties of the carrier are not significantly affected even in the presence of a slight reduction of the particle size.

The treatment of the carrier also causes a significant increase of the fine particle fraction (t Student = 2.42, p < 0.005).

EXAMPLE 2

Preparation of a salbutamol base/lactose binary mixture

25 Analogously to what described in example 1, a mixture containing micronised salbutamol base as active ingredient in a ratio of 200 μ g to 24 mg total mixture was prepared.

The poured and tapped densities and the flowability characteristics were determined as described in example 1.
 30 The dry powder for inhalation was loaded in a Pulvinal^(R) inhaler and the aerosol performances were determined as described in example 1.

The results are reported in Table 3 in comparison with a similar preparation obtained by mixing the active

ingredient with α -lactose monohydrate lactose 90-150 μm not pre-treated in a mixer (standard preparation).

Table 3

5	Standard preparation	Preparation of Example 2	
		Technological parameters	
	Apparent density (g/mL)		
	- Poured	0.71	0.74
	- Tapped	0.78	0.83
	Flodex test (\varnothing 4mm)	4	4
10	Flow Rate through		
	\varnothing 4mm (g/min)	72	-
	Carr Index (%)	9	11
		TSI test	
	Mean weight (mg)	22.2 (1.7)	25.2 (3.3)
15	Emitted dose (μg)	185.0 (2.6)	168.2 (4.7)
	FPD (μg)	60.1 (11.6)	80.9 (14.6)
	FPF (%)	32.2 (11.5)	47.9 (11.4)

Also in this case, the results show that the flowability properties of the carrier do not significantly change.

Analogously, a significant increase ($t = 9.17$, $p < 0.001$) of the fine particle fraction is observed with the carrier prepared according to the process a) described in example 1.

25 EXAMPLE 3

Preparation of a BDP/lactose/magnesium stearate ternary mixture

The powder carrier was prepared according to Example 1 a) by mixing α -lactose monohydrate for 30 minutes in a sigma blade mixer. Afterwards lactose was mixed with 0.25% by weight of magnesium stearate in a Turbula mixer for two hours. Finally the dry powder for inhalation was prepared by mixing an amount of micronised beclomethasone dipropionate corresponding to a dose of 200 μg and the

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carrier (lactose + magnesium stearate) for 30 minutes in a Turbula rotating mixer at 32 rpm.

The poured and tapped densities, the flowability characteristics as well as the aerosol performances were determined as described in example 1.

The results are reported in Table 4 in comparison with a standard formulation obtained by mixing 200 μg of micronised BDP with a carrier powder consisting of 99.75% by weight of α -lactose monohydrate 90 - 150 μg not pre-treated in a mixer, and 0.25% by weight of magnesium stearate (standard preparation).

Table 4

Standard preparation		Preparation of Example 3	
		Technological parameters	
Apparent Density (g/mL)			
5	- Poured	0.76	0.83
	- Tapped	0.81	0.92
	Flodex test (0 4mm)	4	4
Flow Rate through			
	0 4mm (g/min)	56	42
10	Carr Index (%)	6	10
TSI test			
	Mean weight (mg)	24.5 (1.5)	27.9 (3.2)
	Emitted dose (μ g)	188.9 (4.5)	199.8 (2.2)
	FPD (μ g)	48.0 (19.5)	68.9 (5.6)
15	FPF (%)	25.3 (15.3)	34.5 (5.2)

The flowability properties of the carrier do not significantly change even in the presence of a ternary mixture and a significant increase ($t = 8.29$, $p < 0.001$) of the fine particle fraction is observed with the carrier prepared according to the invention.

CLAIMS

1. A process for modifying the surface properties of particles for use as carrier particles for the pulmonary administration of micronised drugs by means of dry powder inhalers, the process including the step of subjecting said carrier particles to a mixing treatment in a mixer equipped with a rotating element in order to produce *in situ* a fine fraction of said carrier.

2. A process according to claim 1, in which the particles of said carrier have a starting diameter ranging from 90 to 150 μm and said fine fraction of the carrier has a mean aerodynamic diameter of less than 10 μm .

3. A process according to claims 1-2 in which the mixer is selected from those with a stationary or rotating body equipped with any rotatory element (blade, screw) or the high energy ones such as "high-shear".

4. A process according to claims 1-3 in which the mixer is a sigma blade mixer and the rate of mixing is comprised between 100 and 300 r.p.m..

5. A process according to claims 1-4, in which the mixing time of the carrier powder ranges from 5 to 360 minutes.

6. A process according to claims 1-5, in which the mixing time is 30 minutes.

7. A process according to claims 1-6, in which said carrier consists of one or more saccharides.

8. A process according to claims 1-7, in which said carrier consists of α -lactose monohydrate.

9. A process according to claims 1-8, which yields a fraction of carrier particles whose variation of the starting mean aerodynamic diameter is less than 20%.

10. A process according to the preceding claims in which, after mixing in the mixer, a suitable amount of an additive selected from lubricants, anti-adherent agents and glidants is added to the carrier.

11. A process according to claim 10, in which the amount of additive ranges from 0.05 to 2%.

12. A process according to claims 10 and 11, in which the lubricant is magnesium stearate, stearic acid, sodium stearyl fumarate or sodium benzoate.

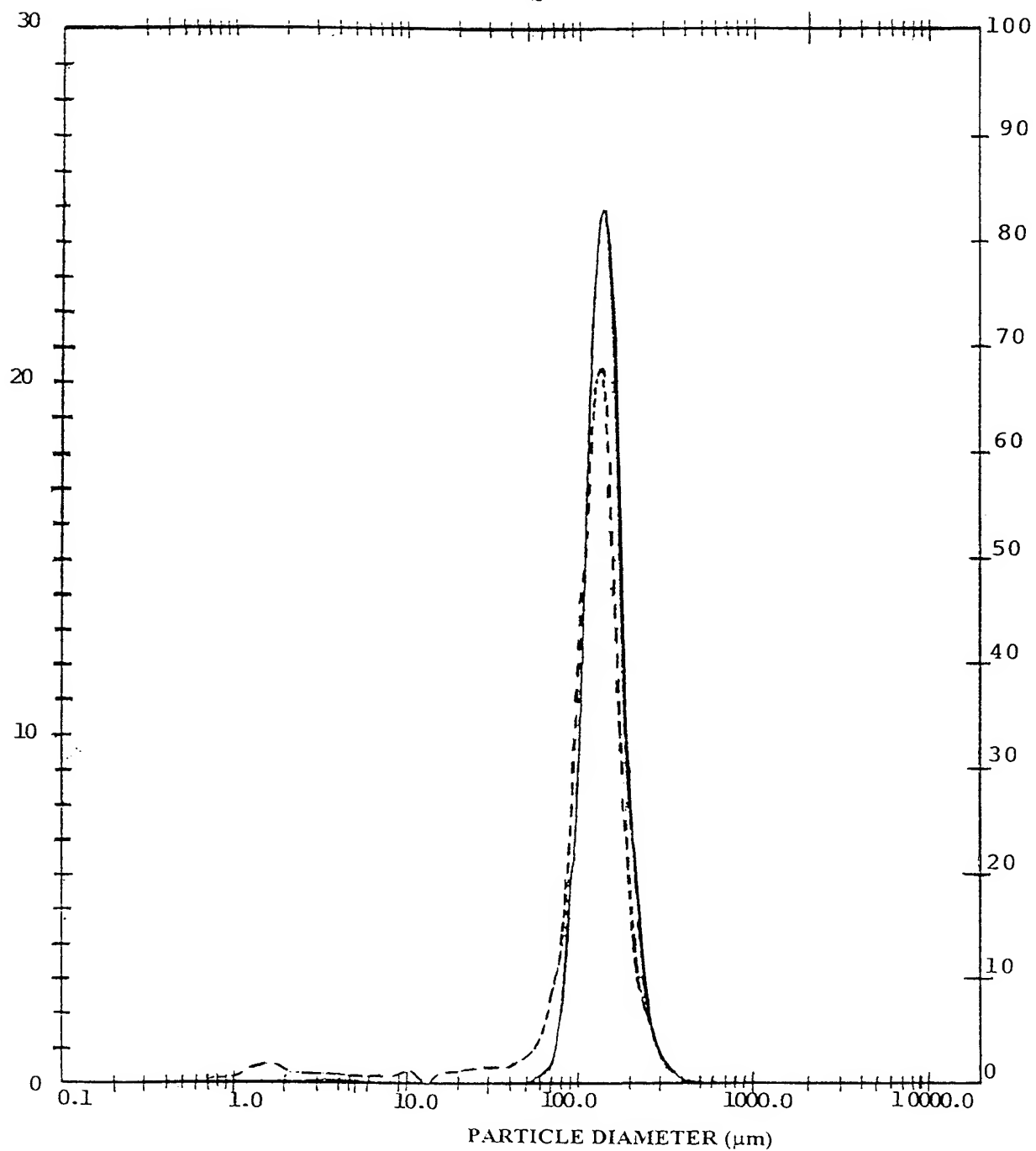
13. A process according to the preceding claims, in which one or more active ingredients, whose particles have a mean diameter of less than 5 μm , are added to the carrier.

14. A process according to claim 13, in which the active ingredient is a β -agonist selected from salbutamol, formoterol, salmeterol, terbutaline or salts thereof.

15. A process according to claim 13, in which the active ingredient is an antiinflammatory steroid selected from beclomethasone dipropionate, flunisolide, budesonide and the epimers thereof.

16. A process according to 13 in which the active ingredient is an anticholinergic selected from ipratropium bromide or oxytropium bromide.

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FIGURE
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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/EP 00/01773

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K9/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 25 255 A (ASTA MEDICA AG) 18 January 1996 (1996-01-18)	1-3,5-9, 13-16
Y	page 2, line 1 - line 5 page 3, line 8 - line 55	10-12
A	WO 95 11666 A (CO-ORDINATED DRUG DEVELOPMENT LTD.) 4 May 1995 (1995-05-04) cited in the application page 12, line 2 -page 18, line 25	1-3,5-9, 13-16
Y	WO 96 23485 A (CO-ORDINATED DRUG DEVELOPMENT LIMITED) 8 August 1996 (1996-08-08) cited in the application claims 1-49 page 12, line 21 -page 13, line 12 page 17, line 8 -page 23, line 7	10-12
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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